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# Normal Organ Radiation Dosimetry and Associated Uncertainties in Nuclear Medicine, with Emphasis on Iodine-131

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**In many medical applications involving the administration of iodine-131 ($^{131}I$) in the form of iodide ($I^-$), most of the dose is delivered to the thyroid gland. To reliably estimate the thyroid absorbed dose, the following data are required: the thyroid gland size (i.e. mass), the fractional uptake of $^{131}I$ by the thyroid, the spatial distribution of $^{131}I$ within the thyroid, and the length of time $^{131}I$ is retained in the thyroid before it is released back to blood, distributed in other organs and tissues, and excreted from the body. Estimation of absorbed dose to nonthyroid tissues likewise requires knowledge of the time course of activity in each organ. Such data are rarely available, however, and therefore dose calculations are generally based on reference models. The MIRD and ICRP have published metabolic models and have calculated absorbed doses per unit intake for many nuclides and radioactive pharmaceuticals. Given the activity taken into the body, one can use such models and make reasonable calculations for average organ doses. When normal retention and excretion pathways are altered, the baseline models need to be modified, and the resulting organ dose estimates are subject to larger errors. This paper describes the historical evolution of radioactive isotopes in medical diagnosis and therapy. We nonmathematically summarize the methods used in current practice to estimate absorbed dose and summarize some of the risk data that have emerged from medical studies of patients with special attention to dose and effects observed in those who received $^{131}I$-iodide in diagnosis and/or therapy.** 

## INTRODUCTION

Nuclear medicine began with the use of radioactivity to trace the absorption, fate and excretion of radioactive isotopes of normal body constituents, such as iodine, potassium, sodium, calcium and iron. With the development of imaging equipment in the early 1950s, imaging of bodily functions proceeded rapidly. Nuclear medicine went on to apply labeled compounds to study biochemical pathways, for example, the delineation of the biokinetic pathways in the Krebs cycle and photosynthesis based on the changing concentration of carbon-14 ($^{14}C$)-labeled molecules.

Diagnostic and therapeutic applications appeared at about the same time. The earliest applications of man-made radioactivity included attempts to treat cancer. The earliest treatment of cancer had used $\gamma$ rays from naturally occurring radium and implanted radon gas seeds in the treatment of uterine cancer. Within 2 years after the first medical cyclotron was installed in Berkeley in 1937, phosphorus-32 ($^{32}P$) was produced and administered in an attempt to treat the first of a small number of chronic lymphocytic leukemia patients.

Clinical applications of radioactive materials, as well as methods to estimate absorbed dose from injected materials, were developed in the course of early patient and animal studies sponsored by the U.S. Atomic Energy Commission. The insights and tools developed in these early studies were improved when advanced imaging devices and computers became available to facilitate more complex calculations. Currently available instruments and mathematical tools facilitate accurate estimation of the radiation doses received by patients undergoing nuclear medicine procedures.

Great interest and active investigation of thyroid function in health and disease led to the early development of tracers and equipment for measuring the uptake and distribution of radioactive iodine and ultimately to its therapeutic use. In 1934, Fermi produced a small amount of $^{128}I$ by neutron bombardment of stable iodine, $^{127}I$, and this was used to measure the accumulation of iodine in the thyroid gland. The properties of $^{128}I$ were not suitable for medical applications, and in 1938, Seaborg searched for and produced $^{131}I$ in response to urging from medical colleagues for a radioactive isotope of iodine with a more suitable half-life and emission energies for clinical use. This was rapidly applied to physiological, diagnostic and therapeutic studies in Berkeley and Boston (MIT/Harvard), and by 1942 medical applications that are still in common use had emerged. A pause occurred during World War II, but after 1945, there was a major effort to produce and distribute large amounts

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of $^{131}$I for a growing list of biomedical applications. The revolution in biochemistry that is now known as molecular biology has emerged from the tracer studies that began soon after World War II.

In this article, we discuss the current state of the dosimetry tools used in medicine to compute organ dose, with a discussion of some of the major sources of uncertainty in these calculations and the confidence that can be assigned to individual and population doses. Special attention is given to $^{131}$I because of its importance in epidemiological studies of radiation exposure among patients and the general public.

## METHODS OF DOSE ESTIMATION

### *Historical Background*

Methods and procedures for calculating dose from external sources and from internally administered radioactivity date back to the earliest years after Roentgen's discovery of X rays. Physicists developed models that were useful for calculating doses from well-defined sources to internal and external targets (*1*). In the early years, there was a concerted effort to standardize activity and measurement methods. The National Bureau of Standards in the U.S. and comparable groups elsewhere provided this important service. Nonetheless, even in the 1940s and 1950s, different values were used by different research centers for such fundamental quantities as the activity of a radionuclide. The need for standardization of methodology led to the development of organ phantoms to facilitate interlaboratory comparisons of organ uptake measurements. The important studies by Brucer *et al.* (*2*) revealed widely varying results among different laboratories and led to the general adoption of standardized methods for acquiring data that reduced interlaboratory variability.

The administration of radioactivity to patients has been supervised from the beginning by physicians relying heavily upon a core group of physicists, engineers and chemists attracted to this fast-growing and important new technology. The rapid development of computers since the 1950s made it possible to calculate the distribution of activity in more realistic geometries than was possible previously. By the end of the 1960s, a high degree of sophistication had emerged in support of the increasing use of ionizing radiations in nuclear medicine practice (diagnosis and therapy). The National Council on Radiation Protection and Measurement (NCRP) (*3–5*) and the International Commission on Radiation Protection (ICRP) (*6, 7*) disseminated reference and guidance materials in support of the medical and industrial uses of different kinds of radiations. With the increasing number and frequency of radiopharmaceutical administrations in many countries came the need for international organizations to collect and tabulate data on patient dose from these medical uses. Estimates of long-term health effects from medical uses of radionuclides, with particular attention to $^{131}$I, have been and are the subject of epidemiology studies in many countries. The sources and effects of radiation have been summarized in periodically updated reports of national and international review bodies, in particular by the United Nations Scientific Committee on the Effects of Atomic Radiation (*8*).

Nuclear medicine imaging procedures are used in all modern medical centers for a wide variety of purposes. A radioactive element injected into the body can be imaged, and its passage through different organs provides information on the transit times through normal and diseased organs. When the radioactive element is used to label a compound that targets a particular organ, then the function of that organ can be assessed by sequentially following the labeled compound. The compounds used for such studies are all FDA-approved radiopharmaceuticals for which the integrity of the labeled compound and its safety and efficacy are certified. Brain, thyroid, parathyroid, heart, lung, liver, spleen, adrenal, kidney, bone, bone marrow, lymphatic organs and receptors on tumors and other foreign substances, such as bacteria, can now be imaged noninvasively with nuclear medicine procedures (*9*). The main advantages are the very high sensitivity of the procedures (the body has negligible radioactive background) and the very high specificity of the targeted radiopharmaceuticals used in regular medical practice. Tables listing many of the radiopharmaceuticals and the amounts used in medical practice are found in ICRP publications (*6, 7*) along with data on the models upon which the calculations are based.

### *General Principles of Dose Estimation*

A listing of the factors required for the estimation of dose is a necessary starting point for a consideration of the inherent problems. One needs to know the amount of radioactivity absorbed into the body by the different routes of entry, the chemical form taken in, the metabolic transformations that influence the subsequent distribution in space and time in the different parts of the body, the size and shape of the organs that contain the radioactivity, and the size and shape of the radiobiologically sensitive targets for which the dose is to be estimated. In medicine, the amount and kind of radioactivity administered is well established, and the anatomy of the patient can be ascertained by noninvasive imaging. The passage of radioactivity through parts of the body can be measured, although chemical transformations that occur are more difficult to establish. A general understanding of the biodistribution can be obtained through measurements of the distribution of radioactivity as a function of time until the material is excreted from the body by urine, stool or other (usually minor) pathways such as exhalation, perspiration and hair formation.

Given knowledge of the biological, physical and chemical factors noted above, one then needs to calculate the pattern of energy absorbed in the different tissues from various radiations ($\alpha$ particles, $\beta$ particles, $\gamma$ rays and X rays)

emitted during the radioactive decay processes for the particular radionuclides administered and any transformations they undergo in the body. The energies and abundances of the radiations emitted during decay for a particular radionuclide generally have the lowest inherent error among these factors. Except for the lowest energy of least frequent emissions (e.g. Auger electrons), these quantities are relatively easy to determine, with uncertainties of 1% or less. Calculation of the energy absorbed in one part of the body per unit energy emitted in another is established by theoretical means [e.g., by assuming that 100% of ''short-range'' emissions (such as $\alpha$ particles or electrons) are entirely absorbed within the region where they are emitted] or through modeling of radiation transport and absorption of more penetrating emissions through analytical means (*10*) or simulation (*11*). To some degree, the uncertainty in these calculations can be controlled, e.g. in a Monte Carlo analysis by increasing the number of particle histories simulated.

There are a number of important differences between organ dose estimates derived from internal emitters (like $^{131}$I discussed herein), and from external X-ray exposures, discussed by Stovall *et al.* (*12*) in this issue. The dose to the thyroid from X-ray tubes falls off at the edges of the field, but it is essentially uniform within the portion of the tissue that is located within the irradiated field. The dose to the thyroid from the internal emitter $^{131}$I depends on its radiation properties and its distribution and retention pattern within the gland. The distribution of the radionuclide may be relatively uniform in the normal thyroid gland, but it can be highly nonuniform in nodule-containing glands, as occurs in persons on iodine-deficient diets. Knowledge of the changing spatial and temporal distribution of radioactivity is needed for internal dosimetry, and this adds a level of complexity to the dosimetry task. The nonuniform uptake of $^{131}$I in iodine-deficient glands is an accepted fact, but the dosimetric consequences are not well established at the cellular level. Theory suggests that in such cases the $^{131}$I particles would tend to deposit energy nonuniformly through an iodine-deficient thyroid gland (*13–17*). If follicles that are undergoing mitotic activity have diminished functional uptake and less active storage of radioactive iodine, lower absorbed doses would be received by radiosensitive cells in follicles undergoing mitosis than would be the case when thyroid follicles are exposed to external radiations, the dose from which is independent of local variations in thyroid function. The extent of such dose disparities could support a relative biological effectiveness (RBE) lower than 1 for $^{131}$I, a hypothesis that is compatible with most animal studies (*18*). The one well-designed animal study that showed an RBE equal to or greater than 1 (*19*) used Long-Evans rats, a poorly inbred strain, which responded differently to $^{131}$I dose than was reported in many studies involving more established strains of rodents.

*MIRD System*

ICRP and MIRD use similar equations, but somewhat different notations, to calculate absorbed doses from internal irradiation. The equation for absorbed dose in the MIRD system (*20*) is given as

$$D_{r_k} = \sum_h \tilde{A}_h S(r_k \leftarrow r_h), \tag{1}$$

where $Dr_k$ is absorbed dose (rad or Gy) in the target region $r_k$ of the body (usually an organ or a tissue) and $\tilde{A}_h$ is the cumulated activity ($\mu$Ci h or MBq s) in a source region $r_h$ of the body. If activity is in units of MBq and time is in units of seconds, $\tilde{A}$ will have units of MBq s. This corresponds to the total number of disintegrations that will occur in the source region $r_h$ over time (i.e., to complete decay). One MBq s is equivalent to $10^6$ disintegrations; 1 $\mu$Ci h is equivalent to $1.33 \times 10^8$ disintegrations.

The factor $S$ takes into account the fact that the absorbed dose in the target region $r_k$ is due not only to the activity of the considered radionuclide in that region but also to the activities in other regions $r_h$ of the body (called source regions). The factor $S$ is expressed as

$$S(r_k \leftarrow r_h) = \frac{k \sum_i n_i E_i \phi_i(r_k \leftarrow r_h)}{m_{r_k}}, \tag{2}$$

where $n_i$ is the number of radiations with average energy $E_i$ emitted per nuclear transition, $E_i$ is the energy per radiation (MeV), $\phi_i(r_k, r_h)$ is the fraction of energy emitted in source region $r_h$ that is absorbed in the target region $r_k$ (absorbed fraction), $m_{rk}$ is the mass of target region $r_k$ (g or kg), and $k$ is the unit conversion factor (rad g/$\mu$Ci h MeV or Gy kg/MBq s MeV).

*Useful Publications and Resources*

To explain and facilitate calculations in their respective dosimetry systems, publications have been developed by the MIRD and ICRP committees. A selected list of MIRD Pamphlets, which are documents usually containing material needed to implement the MIRD system for internal dose calculations, including equations, data, methods, etc., is given in Table 1 (*21*). The MIRD committee also prepared books and dose estimate reports (Table 2). The Radiation Dose Assessment Resource (RADAR) group, which was formed to provide data needed for dose calculations to the user community rapidly and in electronic form (*22*), is also an important source of information.

Most helpful are the tabulations of numerical values for the various quantities in these equations, particularly for the decay data (values of $n_i$ and $E_i$) (*23*), absorbed fractions ($\phi$) (*10*, *24*), and combined factors such as $S$ for selected radionuclides (*25*, *26*).

Absorbed fractions $\phi_i$ are calculated using mathematical representations of the human body, which provide the organ masses (see Eqs. 1 and 2). The first description of a phantom representing the whole body and individual organs of

**TABLE 1**
**Selected MIRD Pamphlets[a]**

| Pamphlet no. | Main topic | Reference(s) | Comments |
|---|---|---|---|
| 1, 1 revised | Estimation of internal doses | (*83*) | Superseded by the MIRD Primer (*20*) |
| 5, 5 revised | Description of anthropomorphic phantom | (*10*, *24*) | Superseded by Phantoms of Cristy and Eckerman (*26*) |
| 11 | *S* values for many nuclides | (*25*) | Newer *S* values are available (*25*) |
| 12 | Discussion of kinetic models for internal dosimetry | (*84*) | |
| 13 | Description of model of the heart | (*85*) | |
| 14, 14 revised | Dynamic urinary bladder model | (*86*, *87*) | Software on SNM Web Site, MIRD Comm. |
| 15 | Description of model for the brain | (*88*) | |
| 16 | Guideline of best practices and methods for collecting and analyzing kinetic data | (*89*) | Widely cited document |
| 17 | *S* values for voxel sources | (*90*) | |
| 19 | Multipart kidney model | (*91*) | |

[a] Based on ref. (*21*).

a reference adult was given in MIRD Pamphlet 5 and the revised version of Report 5 (*10*, *24*). The absorbed fractions derived from Monte Carlo radiation studies using these phantoms were then used to calculate the dose conversion factors (*S* values, as defined above) in MIRD Pamphlet No. 11 (*25*). An improved set of absorbed fractions for a slightly different adult phantom and for five other individuals representing children of different ages (newborn, 1 year old, 5 years old, 10 years old, and 15 years old) was published in 1987 by Cristy and Eckerman (*27*). Then, in 1995, four phantoms representing the adult female, both nonpregnant and at three stages of pregnancy, were published (*28*). The ICRP has adopted the Cristy/Eckerman phantoms for use in calculating dose factors for children and adults for radiopharmaceuticals (*6*, *7*) as well as for population doses from radionuclides (*29*). The MIRD Committee has so far endorsed only its own anthropomorphic phantom from 1975 as acceptable for dose calculations. Nonetheless, dose factors for many radionuclides were developed for most of these phantoms in the MIRDOSE and OLINDA computer programs (*26*, *30*), which have been widely accepted and used by the scientific community. A significant effort is under way to use medical images as the basis for more realistic phantoms (*31*) and more detailed, three-dimensional treatments of radiation dose (e.g. *32*), but this remains a research area at present.

The MIRD Committee has published a handful of documents seeking to establish standardized biokinetics for selected radiopharmaceuticals. The ICRP has produced much of the most useful material in this regard, establishing metabolic models for almost every element (*33*) and over 120 radiopharmaceuticals (*6*, *7*). The ICRP has developed dose conversion factors, which give the cumulative doses absorbed in most organs and the effective dose per unit inhalation or ingestion for many hundreds of radionuclides (*29*, *34*, *35*). These standardized models are helpful in gen-

**TABLE 2**
**Selected MIRD Dose Estimate Reports[a]**

| Report no. | Compound or radiopharmaceutical studied | Reference |
|---|---|---|
| 1 | $^{75}$Se-L-selenomethionine | (*92*) |
| 2 | $^{66}$Ga, $^{67}$Ga, $^{68}$Ga and $^{72}$Ga citrate | (*93*) |
| 3 | $^{99m}$Tc sulfur colloid for liver conditions | (*94*) |
| 4 | $^{198}$Au colloid for liver conditions | (*95*) |
| 5 | $^{123}$I, $^{124}$I, $^{125}$I, $^{126}$I, $^{130}$I, $^{131}$I and $^{132}$I as sodium iodide | (*96*) |
| 6 | $^{197}$Hg and $^{201}$Hg-labeled chlormerodrin | (*97*) |
| 7 | $^{123}$I, $^{124}$I, $^{125}$I, $^{126}$I, $^{130}$I, $^{131}$I and $^{132}$I as sodium rose bengal | (*98*) |
| 8 | $^{99m}$Tc as sodium pertechnetate | (*99*) |
| 9 | Radioxenons in lung imaging | (*100*) |
| 10 | Albumin microspheres labeled with $^{99m}$Tc | (*101*) |
| 11 | $^{52}$Fe, $^{55}$Fe and $^{59}$Fe | (*102*) |
| 12 | $^{99m}$Tc diethylenetriaminepentaacetic acid | (*103*) |
| 13 | $^{99m}$Tc-labeled bone imaging agents | (*104*) |
| 14 | $^{99m}$Tc-labeled red blood cells | (*105*) |
| 15 | Radioindium-labeled antilogous platelets | (*106*) |
| 16 | $^{99m}$Tc diethylenetriaminepentaacetic acid aerosol | (*107*) |
| 17 | $^{81m}$Kr in lung imaging | (*108*) |
| 18 | $^{111}$In-labeled B72.3 | (*109*) |

[a] Based on ref. (*21*).

eral situations, e.g. establishing dose estimates for radiopharmaceuticals or intakes of nuclides by radiation workers. This standardization process typically employs conservative assumptions and mean values for all quantities in the equations above, and thus the tabulated values include substantial uncertainties when applied to specific individuals. Many useful dose factors for radiopharmaceuticals and radiation worker or general population exposure (from inhalation or ingestion of radionuclides) are available in electronic form through the RADAR web site (*22*).

## MAIN SOURCES OF UNCERTAINTY IN THE DOSE ESTIMATES

The reliability of calculated absorbed doses from internal emitters used in medical applications depends in part on the ability to measure and know accurately the amount and kind of radioactive materials taken into the body. Further measurements made using clinical imaging or detection apparatus indicate for how long and in what amounts the radiopharmaceuticals reside in different body regions (organs). Given the chemical form of the labeled compounds, data (albeit not very precisely known) on the distribution of the activity in the different organs, and knowledge of organ mass, one can calculate average absorbed organ dose within a 10% accuracy (*36*). Individual differences in tracer metabolism (kinetics) and anatomy result in broad dose distributions when data based on mathematical phantoms are ascribed to populations about which one has little or no information on anatomy, physiology and the amount of radioactivity that they may have taken in from environmental exposures.

The quantities related to energy emission and absorption are generally associated with low uncertainties. The largest sources of uncertainties in internal dose calculations are typically related to the biokinetic model for a radionuclide or radiopharmaceutical and the physical size and shape of subjects and their organs. People vary considerably in many ways that affect absorbed dose, including nutritional status, medications taken, health status, the size and shape of their organs, exposure to potential carcinogens, and their individual radiosensitivity profiles. Of note is the fact that the biokinetics of many compounds has been determined only in animal populations and extrapolated to humans, with numerous unknowns. The uncertainties of such extrapolations have yet to be studied in any systematic way.

In the end, dose estimates require multiplication and division of the various quantities, so the propagated uncertainties are generally assumed to be represented by a function of the sums of the relative uncertainties squared of each term. Absorbed organ doses are usually given as single values, without associated uncertainties, because the uncertainties in the ''biological'' values often have not been well characterized.

## ESTIMATION OF DOSES FROM $^{131}$I

Among the many radionuclides used in nuclear medicine, $^{131}$I, with a physical half-life of 8.04 days, plays an important role. The metabolism of $^{131}$I administered in iodide form (or in any other common chemical form) is the same as that of stable iodide; and as iodide, $^{131}$I concentrates in the thyroid. In contrast, $^{131}$I administered as a marker attached to a specific chemical compound is subjected to the metabolism of the chemical compound and the $^{131}$I, unless detached from the compound, does not concentrate in the thyroid. To avoid such unintended accumulation, KI is administered to the subject, as discussed in a later section.

The estimation of doses from $^{131}$I administered as iodide for diagnostic purposes, as iodide for therapeutic purposes, and as labeled compounds will be addressed in separate sections.

### *$^{131}$I Administered as Iodide for Diagnostic Purposes*

Iodide metabolism is probably the most studied and best understood metabolic system in the body. Iodine taken into the body is rapidly transferred to blood after oral ingestion, inhalation or topical administration. The thyroid gland very efficiently traps the iodine circulating in blood, most of which, if not taken up by the thyroid, is excreted in the urine, except in the nursing mother, where a substantial fraction goes to milk. The fractional uptake of iodine by the thyroid is typically 0.25 by about 24 h. In the thyroid gland, the iodine is transported into the thyroid follicles where it is incorporated into an iodoprotein (thyroglobulin) containing monoiodotyrosine, diiodotyrosine, tetraiodothyronine (thyroxine or T4), and some triiodothyronine (T3). There are many follicles (typically 150–200 μm in diameter) in the gland, which normally weighs 15–25 g in the adult, depending on the level of dietary intake of stable iodine. The amount of iodide in the circulation that is trapped by the thyroid depends upon the concentration of thyroid hormone in the blood (specifically, unbound thyroxine or free T4) and the resulting levels of pituitary thyrotropin (TSH: thyroid-stimulating hormone). The iodine, in the form of T4 and T3, is slowly released from the thyroid into the blood with a biological half-time of 50 to 100 days (in normal adults). When thyroid hormone levels fall in the blood due to decreased hormone production rates or dietary deficiency of iodine, the level of TSH rises. This positive feedback loop controls the level of thyroid hormone circulating and supplying other organs, where it participates in regulation of cellular metabolic processes. When T3 and T4 are metabolized, the iodine that is released returns to the circulation where once again it can be trapped by the thyroid or by other organs that compete with the thyroid for iodine uptake and excretion. The most prominent of these pathways are the kidneys, the salivary glands, perspiration and milk secretion in the lactating female. Small amounts of milk secretion can also be seen in nonlactating women (galactorrhea).

The size of the thyroid gland varies with many factors, including age, gender and the level of iodine in the diet. The reference values adopted by the ICRP (*37*) for the mass of the thyroid gland are 20 g for the adult male, 17 g for the adult female, 12 g for the 15-year-old child, 7.9 g for the 10-year-old child, 3.4 g for the 5-year-old child, 1.8 g for the 1-year-old child, and 1.3 g for newborn babies. During menarche, the thyroid increases noticeably in size, and in some cases also in iodine uptake (*38*). When dietary levels of iodine are low, the gland is stimulated to trap iodine from the blood more effectively, and the gland may hypertrophy with the development of an enlarged diffuse, nodular or multinodular goiter.

Uptake of radioiodine by the thyroid can be blocked by the administration of stable iodide ion, which dilutes the concentration of iodine perfusing the gland and thereby diminishes glandular uptake of the radioactive atoms. The same effect can be achieved by the administration of thyroid hormone during the time that radioactive iodine is encountered. This is due to the inhibition of TSH, which controls the rate of iodine trapping by the thyroid. These interventions have to be prompt (ideally before radioactive intake occurs) to be maximally effective in reducing radiation dose to the thyroid. Given the same amount of intake into the body, blocking the thyroid, and to a lesser extent the breast uptake, results in more iodine being excreted by the kidneys and bladder, which constitute the major route of excretion (*39*).

Radioactive iodine taken into the mother during pregnancy is partitioned between her normal organs and increasingly with the fetus as development proceeds. Levels of thyroid hormone in the circulation vary during pregnancy, during which time the mother's and baby's needs influence levels of iodine uptake and hormone turnover (*40*). In the fetus, intact thyroid function is very important for normal brain maturation. The influence of fetal thyroid function on brain maturation is complex, because much of the thyroid hormone needed for normal brain development is supplied by the mother. If treated promptly with thyroid hormone after birth, an athyreotic child ordinarily develops ''normally''.

The fetus receives dose from $^{131}$I and from labeled hormone that traverses the placenta as well as from $^{131}$I located in the maternal circulation and the different source organs. The thyroid gland first appears at about the 10th week *in utero* and grows from about 0.02 g at a fetal age of 10 weeks to approximately 1.3 g at term (*37*). Increased accumulation of $^{131}$I has been measured in the human fetal thyroid between weeks 13 and 22, during which time the thyroid dose increases approximately tenfold (*41*). Uptake in the second and third trimesters increases, but data on absorbed dose are less well defined in the later stages of pregnancy. On the basis of a compartment model developed by Berkovski (*42*), the ICRP (*43*) has estimated doses throughout the *in utero* period for various conditions of intake by the mother to be 240 and 680 mGy per MBq of $^{131}$I administered to the mother during the 15th and the 25th weeks after conception, respectively.

During lactation, the breast competes with, and sometimes exceeds, the thyroid in the amount of iodine concentrated therein and secreted in milk. Simon *et al.* (*44*) reviewed the literature related to the estimation of the transfer of $^{131}$I from intake by the mother to human breast milk; a geometric mean value of 0.37 Bq per liter of milk for an intake of 1 Bq per day by a healthy mother was determined. This leads to a thyroid dose to the breast-feeding baby of about 1.2 Gy for an intake of 1 MBq by the mother. Iodine blocking would result in lower concentrations of $^{131}$I in breast milk (*44*). Nonetheless, all responsible groups recommend that breast feeding be discontinued when the mother has an increased intake of $^{131}$I.

Data on thyroid and other organs receiving significant dose from $^{131}$I have been established by various investigators and scientific bodies. For $^{131}$I used in diagnosis, with administered activities of the order of 0.2 MBq, the available biodistribution data obtained in animals and human volunteers, and the *S* values calculated with anthropomorphic models can be simply transposed to patients (*45*). Dose estimates published by the ICRP (*6*) relative to the administration of $^{131}$I as iodide are given in Table 3 separately for various levels of thyroid uptake and for two age groups (infants and adults). All levels of thyroid uptake are assumed to represent basically normal thyroid function: In other words, the value of the thyroid uptake was not assumed to represent a hypo- or hyperthyroid status. Thyroid blocking is assumed in the case of 0% uptake. Absorbed dose from $^{131}$I is presented for the thyroid, bladder wall, breast, stomach wall, ovaries, red marrow, kidney and uterus. As expected, the dose to the thyroid is much greater than that to any other organ or tissue when the thyroid is not blocked. In the case of an adult, the thyroid dose varies from 72 mGy/MBq for a 5% thyroid uptake to 790 mGy/MBq for a 55% thyroid uptake. For a given value of the thyroid uptake, the thyroid doses decrease with increasing age and are about 10 times greater for a 1-year-old child than for an adult. The highest doses per unit intake are estimated for very young babies because of their small thyroid mass and the elevated fractional thyroid uptake that is observed soon after birth. Van Middlesworth (*46*) measured fractional thyroid uptakes of about 0.7 in babies who were several days old. This corresponds to a thyroid dose per unit intake or administration of 13.5 Gy/MBq.

In comparison, doses to organs and tissues other than the thyroid are much smaller; the results presented in Table 3 show that they do not exceed a few mGy/MBq for any age and level of thyroid uptake. Salivary gland uptake is clearly manifest in imaging studies, and many patients given large doses during the therapy of metastatic thyroid cancer have sialadenitis (pain due to inflammation of their salivary glands), but there are few published data on iodine kinetics in the salivary gland. Johansson *et al.* (*47*) have presented a model including data for salivary glands for intake of ra-

**TABLE 3**
**Absorbed Doses per Unit Intake of $^{131}$I as Iodide (mGy/MBq) for a Number of Organs and Tissues and for a Range of Values of Thyroid Uptake from Blood (*6*)**

| | Fractional uptake from blood | | | | | | |
|---|---|---|---|---|---|---|---|
| Organ/tissue | 0% | 5% | 15% | 25% | 35% | 45% | 55% |
| | Absorbed doses per unit intake for a one-year-old infant | | | | | | |
| Bladder wall | 3.4 | 3.2 | 2.9 | 2.6 | 2.3 | 1.9 | 1.6 |
| Breast | 0.17 | 0.17 | 0.25 | 0.32 | 0.40 | 0.49 | 0.56 |
| Kidneys | 0.31 | 0.29 | 0.29 | 0.27 | 0.29 | 0.29 | 0.29 |
| Stomach wall | | 2.9 | 2.9 | 3.0 | 3.0 | 3.0 | 3.0 |
| Ovaries | 0.24 | 0.26 | 0.26 | 0.26 | 0.27 | 0.28 | 0.27 |
| Red marrow | 0.20 | 0.18 | 0.24 | 0.29 | 0.35 | 0.41 | 0.46 |
| Thyroid | 0.20 | 680 | 2000 | 3400 | 4700 | 6100 | 7400 |
| Uterus | 0.30 | 0.31 | 0.31 | 0.30 | 0.30 | 0.31 | 0.30 |
| | Absorbed doses per unit intake for an adult | | | | | | |
| Bladder wall | 0.61 | 0.58 | 0.52 | 0.46 | 0.40 | 0.34 | 0.29 |
| Breast | 0.033 | 0.031 | 0.043 | 0.055 | 0.067 | 0.079 | 0.091 |
| Kidneys | 0.065 | 0.063 | 0.06 | 0.058 | 0.056 | 0.053 | 0.051 |
| Stomach wall | | 0.45 | 0.46 | 0.46 | 0.46 | 0.46 | 0.46 |
| Ovaries | 0.042 | 0.044 | 0.043 | 0.043 | 0.042 | 0.042 | 0.041 |
| Red marrow | 0.035 | 0.038 | 0.054 | 0.07 | 0.086 | 0.10 | 0.12 |
| Thyroid | 0.029 | 72 | 210 | 360 | 500 | 640 | 790 |
| Uterus | 0.30 | 0.055 | 0.054 | 0.052 | 0.050 | 0.048 | 0.046 |

dioiodines by adults. Their estimate of 0.50 mGy/MBq of administered $^{131}$I is close to the value estimated previously by Edmonds and Smith (*48*). The dose estimates of Johansson *et al.* (*47*) for adults for other organs and tissues are essentially the same as those reached by ICRP (*6*) with a few exceptions. Johansson et al. (*47*) estimated the dose to the stomach wall at 1.2 mGy/MBq (2.6 times higher) and the dose to the thyroid at 490 mGy/MBq instead of 500 mGy/MBq. They also added an estimate of the testes dose at 0.03 mGy/MBq. They presented no data for children.

Dose to the parathyroid parallels that received by the thyroid, but it depends on the size and spatial relationship between the two glands. The parathyroid is located near or partly embedded in the posterior part of the thyroid gland. The parathyroid dose will be less than that received by the thyroid because of absorption, in the layer of tissue separating the two glands, and the range/energy distribution of the β-particle radiation emitted by $^{131}$I in the thyroid.

### *$^{131}$I Administered as Iodide for Therapeutic Purposes*

The main therapeutic uses of $^{131}$I are for the treatment of hyperthyroidism, with an administered activity typically in the range of 185 to 370 MBq, for an intended thyroid dose of approximately 70 Gy, and thyroid cancer, for which higher doses are delivered, depending on the stage and extent of disease. Administered activities range from 1 to 3.7 GBq to destroy tumor remnants after incomplete surgery and from 3.7 to 10 GBq to ablate remaining localized tumor, while higher administered activities are used to treat patients with persistent metastatic disease.

Some physicians use rule-based guidelines to determine the amount of $^{131}$I to be administered, while others base dose prescriptions on patient-specific measurements (*45, 49*). Despite the fact that such studies have been conducted for a number of years, there is still little agreement on how best to use the information derived or even if such information results in improved outcome relative to that of thyroid cancer patients treated ''non-dosimetrically'' (i.e., with a fixed administered activity of $^{131}$I-iodide). The argument in favor of obtaining detailed dosimetry data is based on the belief that therapeutic doses may be optimized to minimize acute toxicity as well as cancer risk and to maximize efficacy once dose–toxicity and –efficacy relationships are derived from follow-up of dosimetrically treated patients.

In the treatment of patients with uncomplicated Graves' disease, the amount of $^{131}$I typically administered is intended to deliver a thyroid dose of approximately 70 Gy in an attempt to inhibit hormonogenesis. Larger amounts of $^{131}$I are administered to more complicated patients, including those with nodular glands who typically receive higher doses, in the range of 100 Gy or more. The activity to be administered can be determined from measurements of the thyroid mass, fractional thyroid uptake, and biological half-time of residence of $^{131}$I in the thyroid:

1. The estimation of the thyroid mass, especially for abnormally large or abnormally shaped glands, is a major source of error. The best approach uses three-dimensional ultrasound.
2. The thyroid uptake can be calculated from the administered activity and of the net $^{131}$I count rate from the thyroid measured using either a γ-ray probe or γ-ray camera.
3. The biological half-time of residence of $^{131}$I in the thyroid can be obtained from daily measurements of the $^{131}$I

activity that remains in the thyroid, using the same γ-ray probe, from 1 to 7 days after administration of the activity. In most patients with hyperthyroidism, the biological half-time of residence of $^{131}$I in the thyroid is about 20 days, but about 15% of hyperthyroid patients have a more rapid turnover rate because of a small thyroidal iodine pool, resulting in values of the biological half-time of residence of $^{131}$I in the thyroid of about 5 days. In those patients, the level of serum protein-bound $^{131}$I can be very high, resulting in high doses to blood and, by extension, to bone marrow. A more complete dosimetric analysis of small-pool hyperthyroidism can be found in Zanzonico *et al.* (*50*).

In the case of thyroid cancer, the first step in $^{131}$I therapy after thyroidectomy is to ablate any remaining normal thyroid tissue by administration of sufficiently large doses of radioiodine. The administered activity is usually in the range from 1 to 5 GBq. The determination of the activity is derived from the estimation of the thyroid mass, fractional thyroid uptake, and biological half-time of residence of $^{131}$I in the thyroid, as described above, however, because of its smaller size, the mass of residual normal thyroid tissue is more difficult to determine than in patients with hyperthyroidism. Different factors influencing the treatment of remnants have been reviewed by Hay *et al.* (*51*).

Radioiodine treatment of metastatic thyroid cancer after the complete removal of normal thyroid tissue by surgery and/or remnant ablation is accomplished in different ways. Most thyroid cancer therapy is administered using formula-based rules with minimum patient-specific dosimetry. Some academic centers with strong dosimetry programs collect detailed information on the uptake and turnover of a test dose to determine the amount of therapy to be administered. Despite the fact that such studies have been conducted for a number of years, there is still little agreement on how best to use the information derived. The argument in favor of obtaining detailed dosimetry data is based on the belief that this information when correlated with observed sequelae will lead to improved practice guidelines (*52*).

A generally held treatment philosophy by those who do detailed dosimetry is that the tumor dose should be as high as possible while limiting the blood dose to 2 Gy. Briefly, serial time-activity measurements are made of blood, tumor and total-body activity after administration of a tracer dose of about 200 MBq of $^{131}$I. The results are used to calculate the absorbed doses in blood, normal organs and tumor (*53*). The actual therapeutic administered activity is then scaled from those dose levels, keeping in mind that the blood dose should not exceed 2 Gy. After administration of the therapeutic activity, which is usually in the range from 4 to 20 GBq, serial time-activity measurements are then repeated for blood, tumor and total body. The resulting absorbed doses are then analyzed to determine whether the blood dose limit of 2 Gy has been attained or whether re-treatment will be needed if the tumor absorbed dose is substantially less than expected. In fact, experience has shown that in individual patients with widely disseminated metastatic thyroid cancer, the therapeutic dose actually absorbed by the tumor is less than would have been estimated from measurements after the administration of the tracer dose (*54*). The explanation is that even diagnostic doses of the magnitude used clinically result in sufficient radiation damage (stunning) to diminish uptake of the therapy dose. An excellent review of clinical issues involved in thyroid cancer therapy is presented by Robbins and Schlumberger (*55*). Various methods have been used to increase lesion uptake, including diets deficient in iodine, TSH administration and more recently the administration of recombinant TSH (*56*), as well as the use of lithium to prolong retention of $^{131}$I in the tumor (*57*). Improvements in the accuracy of $^{131}$I dosimetry have been achieved using high-energy collimators and improved analysis methods (*36*). Further improvement can be achieved using the PET tracer $^{124}$I, which results in improved dosimetry accuracy (*58*).

### *$^{131}$I-Labeled Compounds*

Many molecules have been labeled with radioactive iodine, and their biodistribution has been followed by measurements in blood and tissue samples as well as by radioactivity measured by external counting probes over the regions of the body of interest, and currently by high-resolution imaging devices. Labeled hormones, drugs and receptor targeting agents are used to study the properties of these agents and their role in health and disease. The ability to do repeated studies with one or multiple injections provides the opportunity for dynamic analysis in resting and stressed states; this facilitates the evaluation of pharmacokinetics in a noninvasive manner as well as the estimation of parameters describing physiological processes, including physiological reserve. Current medical practice uses $^{131}$I-labeled compounds for diagnostic and therapeutic purposes. For diagnostic purposes, $^{123}$I is used increasingly because it produces better images while delivering a lower dose to the patient. $^{131}$I is still used as a treatment planning prelude in an effort to plan the amount needed to deliver an adequate therapy dose. $^{131}$I is used in diagnosis and therapy of cancer using drugs that target receptors on the tumor cells. $^{131}$I-labeled MIBG (metaiodobenzylguanidine) is used in the therapy of neuroendocrine tumors that are found in imaging studies to have avid receptors for the drug. A number of radioactive antibodies labeled with $^{131}$I or other β-particle-emitting radionuclides or α-particle-emitting radionuclides are used in the treatment of different cancers. Other iodine-labeled compounds use positron emissions from $^{124}$I to provide higher-resolution images and more accurate quantitative data for dosimetry studies than can be obtained with $^{131}$I for reasons related to the current state of the art in imaging devices. Whenever large doses of $^{131}$I-labeled drugs are administered in therapy, potassium iodide (KI) is administered prior to and for several days after administra-

tion. When KI is administered prior to $^{131}$I intake, this greatly reduces thyroid uptake and dose to the thyroid.

After the administration of 0.74 MBq of $^{131}$I MIBG, the highest organ dose is received in the liver and is about 0.82 mGy. Detailed information on age-dependent dose coefficients for a number of organs and tissues is provided in ICRP Publications 53 (*6*) and 80 (*7*).

## MAIN SOURCES OF UNCERTAINTY IN $^{131}$I DOSE ESTIMATES

The major contributors to the uncertainty of thyroid dose estimates have been assessed mainly in the framework of environmental studies in which labeled compounds are not considered (*59–61*). For example, Apostoaei and Miller (*59*) estimated uncertainties in the radiation dose estimates for ingestion of $^{131}$I in a soluble form. They evaluated the variables that can influence the uncertainty of reported doses and identified the following important contributors:

1. The ''apparent'' biological half-time of iodine in the thyroid—a lognormal distribution with a geometric standard deviation of 1.8 around central values of 15 days for newborns, 20 days for children, 50 days for adolescents, and 85 days for adults.
2. The uptake fraction of activity from blood, which was fitted with a log-triangular distribution with central values of 0.45 for newborns, 0.37 for children, 0.35 for adolescents, and 0.25 for adults.
3. The thyroid mass, for which they assigned a lognormal distribution with a geometric standard deviation of 1.5 around central values that varied with the age of the individual between early ages and adulthood.

For all ages, the major contributors to thyroid dose were the thyroid mass and the thyroid fractional uptake. Biokinetic parameters related to release of iodine from blood and from the thyroid were smaller contributors, suggesting that the emphasis on reducing uncertainties should be focused on knowledge of thyroid mass and iodine uptake. Similar findings were reported by Aydogan *et al.* (*62*), who identified the thyroid mass as the primary contributor to uncertainty in dose coefficients for ingestion of $^{131}$I, with biokinetic data making a lesser contribution.

It should be noted that the available information is the average activity concentration in the measured organs and that there is likely to be a substantial difference between the true distribution within the gland macroscopically and at the cellular level. Heterogeneity causes the greatest problems when estimating dose from $\alpha$ particles and low-energy electron emitters. Given the high-energy electron emission spectrum from $^{131}$I this is less of a problem in general, except in cases where there is extreme heterogeneity as in nodular goiters and in persons with iodine-deficient diets. Nonuniform uptake of $^{131}$I can be seen on autoradiographs (*63, 64*), with some regions having up to 50 times the average concentration in the gland (*13*). This could be a significant problem in correlating absorbed dose in heterogeneous subregions of the gland in persons (children) in iodine-deficient areas (*65, 66*), which could account in part for the increased risk observed in such individuals.

## RISKS FROM MEDICAL TREATMENT AND DIAGNOSIS INVOLVING INCORPORATION OF $^{131}$I

Early experience with medical uses of $^{131}$I revealed the high concentration of radioactive iodine in the thyroid gland; this was used in the late 1930s for diagnosis and in the early 1940s for treatment of thyroid disease. With the development of nuclear reactors, it was recognized in the 1950s that $^{131}$I was a fission product that could have deleterious health implications if released into the environment in large amounts. In fact, $^{131}$I released from the nuclear fuel cycle is now one of the main concerns from peaceful uses of nuclear energy. Absorbed doses from radioactive isotopes are delivered at much lower dose rates than those from the X and radiation delivered by the atomic bomb, and hence the need for human data on the risk from low-dose-rate radiations was recognized early on.

By the 1960s, large numbers of patients with hyperthyroidism (thyrotoxicosis) had been treated, mostly in major medical centers in the U.S. and other countries. Hyperthyroidism was treated with radioactive $^{131}$I (occasionally with $^{125}$I), surgery or antithyroid drugs, and since the patients generally lived a normal life span, it was decided that a large group of hyperthyroid patients treated with $^{131}$I therapy should be studied. Twenty-six institutions, 25 in the United States and one in the United Kingdom, pooled their rosters of treated patients and embarked on a prospective follow-up using the same protocol. Dosimetry data were extracted from the records. All had known amounts of $^{131}$I administered (activity ranged from 70 to 600 MBq). Many had received several measurements of thyroid uptake, and a small number had detailed kinetic studies on both diagnostic and therapy doses. The protocol was finalized in 1962, and the study was continued through 1968. Reports of the first results were based on follow-up of approximately 22,000 patients treated with $^{131}$I and about 14,000 treated surgically or solely with antithyroid drugs. Some patients had multiple treatments for one or more recurrences of the disease.

The results of the studies revealed a small increase in leukemia in $^{131}$I-treated subjects when compared to age-matched U.S. rates, but the rates in the $^{131}$I-treated patients were less than those observed in the surgically treated patients (*67*). A high rate of hypothyroidism was seen in all groups of treated subjects, regardless of therapy (*68*); however, there was a strong relationship between the amount of $^{131}$I activity and the frequency of hypothyroidism. The study clearly demonstrated the importance of the inclusion of an appropriate comparison group, because without it the small leukemia increase observed would have been attributed to the then estimated 50 to 100-mGy marrow dose

from $^{131}$I rather than to thyrotoxicosis. Additional information was gathered on the frequency of benign and malignant thyroid neoplasms (*69*). No evidence of an increase in malignant thyroid tumors was observed when disease observed in the first 5 years of follow-up was excluded. By excluding these 5 years, the co-occurrence of already present thyroid cancer was not attributed to the $^{131}$I therapy. In 1974, 497 nodules were present when the paper by Dobyns *et al.* was published (*69*). The charts of these patients were reviewed in the mid-1980s by the physicians at the four largest centers, and more than 95% of the cases were instances in which one reviewer noted a nodule, which was not subsequently noted in the patient's chart.[2]

Due to limited information on the biological turnover of $^{131}$I in the subjects in the original thyrotoxicosis therapy study, organ doses could not be estimated, and therefore administered activity was used as a measure of exposure. The amount of activity administered in single doses ranged from $<$185 MBq to $>$555 MBq. Assuming 25–50% uptake in adults, and given a mean activity of 330 MBq of $^{131}$I administered to the patients who developed leukemia, the bone marrow dose is estimated using ICRP data to lie between 13 and 67 mGy.

A later follow-up of cancer mortality was conducted on this same patient population (*70*). The study revealed that the total number of cancer deaths was close to that expected based on mortality rates in the general population (2950 compared to 2857), but there was a small excess of mortality from cancers of the lung, breast, kidney and thyroid. A deficit of deaths was noted for cancers of the uterus and the prostate gland. Radioactive iodine was not linked to total cancer deaths or to any specific cancer with the exception of thyroid cancer; however, thyroid cancer risk was not elevated when the first 5 years of follow-up were excluded. While this study does not provide compelling evidence for an association between $^{131}$I therapy given to adult patients and thyroid cancer mortality, it should be noted that because thyroid cancer is rarely fatal, mortality is not a good measure of the effects of $^{131}$I on the thyroid gland. While a British study of hyperthyroid patients found a small but significant increased risk of thyroid cancer incidence and mortality among $^{131}$I-treated patients (*71*), a Swedish study reported that the risk of thyroid cancer was not significantly elevated 10 or more years after treatment (*72, 73*).

Thyroid cancer risk also has been examined in cohorts of patients receiving diagnostic $^{131}$I examinations (*74–77*). No significant excess risk of thyroid cancer was demonstrated among patients who were examined for reasons other than a suspected thyroid tumor, even though the mean thyroid doses are about 0.9 Gy.

In the most recent follow-ups of hyperthyroid patients, neither leukemia risk nor other malignancies have been significantly linked to $^{131}$I therapy (*70, 71*), but the doses to organs other than the thyroid are quite low.

$^{131}$I is also frequently used as a treatment for thyroid cancer. The thyroid doses for this therapy are extremely high, with the aim of killing all of the cells in the thyroid tissue. The doses to other organs are generally small. In a follow-up of Swedish thyroid cancer patients treated with $^{131}$I, the red bone marrow dose was estimated to be about 251 mGy (*73*). Leukemia risk has been elevated in some cohorts of thyroid cancer patients treated with $^{131}$I (*78, 79*), but not all (*74*). To shed more light on the risks from the $^{131}$I treatment, a pooled analysis of three European (Sweden, France and Italy) cohorts was conducted (*80*). The mean administered activity was 6 (0.2–56) GBq. The risk of leukemia was elevated, but it did not reach statistical significance (RR = 1.9; 95% CI = 0.8–3.6). In the pooled analysis, there was also suggestive evidence of an increased risk of cancers of the salivary gland, bone and soft tissue, and uterus. No evidence of genetic effects in the offspring of women treated with $^{131}$I for thyroid cancer has been detected (*55*), but the recommendation that conception be delayed for 1 year after therapy is still advocated.

It is generally agreed that no evidence of significant germ cell damage (such as impaired fertility and increased of birth defects) has been noted among subsequently conceived offspring of $^{131}$I-treated hyperthyroid patients. Nonetheless, demonstrable gonadal damage, specifically, transiently impaired fertility, may occur occasionally among thyroid cancer patients treated with much larger amounts (greater than 3.7 GBq) of $^{131}$I (*81, 82*).

## CONCLUSIONS

The development and use of radioactive isotopes of iodine has improved medical care substantially. Many clinical applications were an outgrowth of the development of the technology and the biological knowledge it engendered. Concern regarding the safe and effective use of radiation in medicine led to the development of standardized procedures and methods for calibrating the amount of activity administered to patients. This included much attention to quality control of the radionuclides administered, their chemical and radionuclidic purity, and their stability in the body.

Dosimetry systems for intake of radionuclides evolved from simple mathematical models to complex computer-based systems that provide high accuracy. These methods are in routine use in all major medical centers. With these tools, many investigations have led to the publication of high-quality data on radiation dose to patients, to workers, and to the public from environmental releases of many radionuclides. $^{131}$I has received the greatest emphasis because of its unique applications in medicine and its major role in planned and unplanned releases from nuclear power plants and from fallout from weapons testing.

[2] A. B. Brill, Review of charts from Mayo Clinic, Cincinnati General Hospital, New York hospital, and Cleveland Metro General Hospital. Personal communication, 1986.

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